REMARKS:

Claims 1-10, 13 and 14 are in the case and presented for consideration.

Claim 1 has been amended to address the Examiner's rejections under 35 U.S.C. 112, first and second paragraphs, and under 35 U.S.C. 101.

Support:

For better reference, following is amended claims 1 with sections from the specification included in brackets where support for the key features of the claim can be founds:

Claim 1. A method for measuring the phosphorylation state [page 8, line 33] of biological molecules in a sample, comprising tagging these molecules with fluorescent markers and activating these fluorescent markers by irradiating the sample with light, the method further comprising the steps of:

(a) selecting a fluorescent marker, whose fluorescence lifetime assumes a different value depending upon the presence or absence of phosphate groups in its vicinity [page 4, lines 9-11; page 6, lines 18-19 and 21-23];

(b) attaching the fluorescent marker selected in step (a) to a biomolecule [page 4, lines 19-20];

(c) measuring the fluorescence lifetime of the fluorescent marker in a sample containing [page 1, line 33; page 8, line 12] the biomolecule with the fluorescent marker [page 6, lines 21-23] attached in accordance with step (b); and

(d) classifying the biomolecules in the samplein accordance with the presence or absence of phosphate groups attached to said biomolecules, while

basing said classifying on the different lifetime of each fluorescence marker.

The title has also be corrected to address the Examiner's objection to the title and a correction has been made to the specification on page 8 to better explain the invention.

In claim 1, the phrase "measuring the presence or absence of phosphate groups attached to" has been replaced by the technical synonym "phosphorylation state." This directly points to the present invention, which is a direct method to monitor the phosphorylation state of biomolecules.

The method of Claim 1 now includes four further steps, i.e.: (a) selecting particular fluorescent markers; (b) attaching these fluorescent markers to biomolecules; (c) measuring the fluorescence lifetime of the attached fluorescence markers; and (d) classifying the biomolecules in groups with or without attached phosphate group.

In the interests of explaining the invention in more detail:

Figure 1 of the application as filed shows the lifetime of the fluorescence marker attached to a polypeptide (tracer peptide without enzyme activity) containing a phosphate group. The lifetime is drawn versus the concentration of an enzyme that is added to the sample, which contains the polypeptide/fluorescent marker aggregate. As described in the specification as filed (see page 8, line 8 and line 27 to page 9, line 18) phosphatase molecules have been used as the enzyme in this experiment.

Phosphatases are known to cleave a phosphate group into water (see page 5, lines 26-27). Thus, the phosphatase enzyme added to the sample with the labeled tracer peptide will cleave the phosphate group and dephosphorylate the tracer peptide. The more

phosphatase enzyme is added to the sample the more pronounced will be this dephosphorylation process. On the left side of the graph in Figure 1, the longer lifetime of the fluorescence marker attached to the tracer polypeptide of about 3110 pico seconds therefore shows the tracer polypeptide in its phosporylated state. On the right side of the graph in Fig. 1, however, the shorter lifetime of the fluorescence marker attached to the tracer polypeptide of about 2950 pico seconds shows the tracer polypeptide in its dephosporylated state (see page 9, lines 4-6). Figure 1 therefore clearly shows the difference in the lifetime of the fluorescent label according to the presence or absence of a phosphate group in a bio-molecule (see page 9, lines 8-18).

Difference over the prior art:

It is expressly pointed out that no auxiliary molecule (like an antibody) was needed to be attached to the bio-molecule in order to do this classification of the tracer polypeptide into its two different phosphorylation states. In the paper by Fowler et al., always an antibody needed to be used (see the entire second paragraph of the paper and Fig. 1). The disclosure of Fowler et al. thus clearly falls under the prior art as it is described in the specification as filed (see page 2, lines 1-33). In contrast, the advantage of the present invention is that no auxiliary molecules, like e.g., antibodies, need to be used for the classification of a biomolecule according to its phosphorylation states (see page 6, lines 21-28 and page 8, lines 29-31).

Novelty and unobvious steps:

With these explanations, the gist of the invention is clear as is the difference over

the prior art (including Fowler et al.). There is no hint in the prior art that would direct a skilled person to propose the present invention. The fact that special fluorescent markers had to be found that exhibit the particular function as now clearly defined in the amended claim 1 is a serious indication of the presence of an inventive step.

Thus, the amended claim 1 is believed to be novel and unobvious over the prior art cited by the Examiner.

Disclosure of fluorescence lifetime measurements:

Applicants respectfully point out that measurement of the fluorescent lifetime is a method that is very well known *per se* (see for example Fowler et al.) and does not need to be explained in more detail.

Dependent claims 2-10 further distinguish the invention over the prior art, as do added claims 13 and 14 which have been added to re-introduce features of amended claims 2 and 5 which were amended to improved their form.

Claims 11 and 12 have been canceled.

Accordingly the application and claims are now believed to be in condition for allowance and favorable action is respectfully requested.

If any issues remain which may be resolved by telephonic communication, the Examiner is respectfully invited to contact the undersigned at the number below, to advance the application to allowance.

Respectfully submitted,

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